REMARKS

Reconsideration of the present application is respectfully requested in view of the above Amendments and the following remarks. Claims 25, 29, 31, 32, 35, 40, 41, 43, 50, 51, 57, 59, 60, 62-67, and 69-72 are pending and under examination. Applicants acknowledge and thank the Examiner for indicating that claims 25, 32, 35, 40, 41, 43, 60, 64, and 67 are allowable. Applicants have amended claims 29 and 31 for clerical purposes point out with greater particularity and distinctly claim certain embodiments of Applicants' invention. No new matter has been added to the application by these Amendments.

Applicants submit herewith a Supplemental Information Disclosure Statement. Applicants respectfully request consideration of the cited references and entry of the references into the record.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

The Examiner rejected claims 29, 31, 50, 51, 57, 59, 62, 63, 65, 66, and 68-72 under 35 U.S.C. § 112, first paragraph, asserting that the claims are directed to subject matter that is not adequately described in the specification. The Examiner states that the rejection is maintained for the reasons asserted in the previous Office Action.

Applicants traverse this rejection and submit that the present application and instant claims comply with the written description requirement by describing the claimed subject matter to a person skilled in the art using sufficiently detailed, relevant, identifying characteristics such as functional characteristics, and correlating those functional characteristics with the disclosed structure. *See* M.P.E.P. § 2163.II.A.3; *Enzo Biochem v. Gen-Probe*, 323 F.3d 956, 964, 967, 968 (Fed. Cir. 2002). The present claims are directed, in pertinent part, to an isolated recombinant polypeptide comprising an immunogenic fragment of 15 or more contiguous amino acids of SEQ ID NO:2, wherein the polypeptide is capable of inducing an antibody that specifically binds to the fragment within SEQ ID NO:2, and to related fusion proteins and immunogenic compositions comprising the recombinant polypeptides.

Written description is adequate when the specification describes the claimed embodiments in sufficient detail to convey *to a person skilled in the art* that the Applicants were in possession of the claimed embodiments at the time of filing, even if each and every species

encompassed by the claims is not explicitly described in the specification. *See, e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991), citing *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). As suggested by *Vas-Cath*, applying a rigid framework would not be appropriate when ascertaining whether a particular written description is sufficient. The Federal Circuit Court of Appeals has articulated that with respect to the biological art, "[p]recedent illustrates that the determination of what is needed in a specification to support generic claims related to biological subject matter depends on a variety of factors, including existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter" (*Capon v. Eshhar,* 418 F.3d 1349, 1359 (Fed. Cir. 2005), citing *In re Wallach*, 378 F.3d 1330, 1333-34 (2004); *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 925 (Fed. Cir. 2004); *Singh v. Brake*, 317 F.3d 1334, 1343 (Fed. Cir. 2003); *see also* M.P.E.P. § 2163.02). Therefore, the fundamental factual inquiry in determining adequacy of the written description focuses on the understanding of *a person skilled in the art* and whether *a person skilled in the art* would understand that Applicants were in possession of the claimed embodiments.

A person skilled in the art would readily appreciate that the specification sufficiently describes the species encompassed by the claims, given the exemplary, recited amino acid sequence, SEQ ID NO:2, of a full-length *Neisseria meningitidis* polypeptide (referred to as BASB082 in the application). By providing the detailed chemical structure, that is, the amino acid sequence (*i.e.,* SEQ ID NO:2), the present application therefore discloses the structure of polypeptide fragments consisting of 15 or more amino acids of SEQ ID NO:2 (*see also, e.g.,* page 5, second full paragraph; page 10, second paragraph). The specification further describes that an immunogenic fragment of a BASB082 polypeptide is a contiguous portion of the BASB082 polypeptide that has the same or substantially the same immunogenic activity as the polypeptide of SEQ ID NO:2, which includes the capability of raising an immune response, which includes production of antibodies, that specifically recognizes the exemplary BASB082 polypeptide disclosed therein (*see, e.g.,* page 5, second full paragraph).

The specification further describes that certain tertiary characteristics can be predicted on the basis of the amino acid sequence (*see* page 83, Example 1). BASB082 is

predicted to be an outer membrane protein that may be involved in iron uptake. The BASB082 polypeptide has a predicted leader signal peptide sequence, which would be cleaved after amino acid residue 24 of the sequence set forth in SEQ ID NO:2. As is well understood in the art, polypeptides that are membrane bound proteins are translocated through or to the membrane, respectively, by a translocation apparatus that interacts with a signal peptide at the amino terminal end of a nascent polypeptide. A signal peptide sequence is typically cleaved from a nascently translated polypeptide in vivo by a bacterial protease to form the mature polypeptide. The specification further describes that an immunogenic polypeptide fragment may include a BASB082 polypeptide that is *lacking* the N-terminal leader sequence, and/or a transmembrane domain, and/or a C-terminal anchor domain.

Applicants have described the recited structural features of the claimed recombinant polypeptides comprising an immunogenic fragment according to common terminology used in the art and have correlated the structural features with the recited functional characteristics (*i.e.,* capability to generate an antibody that specifically binds to the fragment sequence within SEQ ID NO:2). Thus, in view of the state of the art, given the present description and the high skill level of a person skilled in the art, the skilled person could envision and readily predict that many species would be operable other than those disclosed. Applicants therefore disagree with the assertion in the prior Office Action (dated October 27, 2008, at page 4) that the claimed subject matter is defined only by a functional characteristic.

By contrast to the present claims, the claims at issue in *The Regents of the University of California v. Eli Lilly and Company* (119 F.3d 1559 (Fed. Cir. 1997)), to which the Office Action (dated October 27, 2008) refers, did *not* recite *any* amino acid or nucleic acid sequence, structure, or formula. Moreover, the Federal Circuit Court of Appeals, confirming that in *Eli Lilly* the term, "human insulin cDNA," conveyed no relevant structural or physical characteristics, further stated that, "[i]t is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement" (*see Enzo Biochem* at 964; *see also Amgen Inc. v. Hoechst Marion Roussel, Inc.,* 314 F.3d 1313, 1332 (Fed. Cir. 2003)). A disclosure naming a single species can support claims to a genus if, as here, the disclosure conveys to a person skilled in the art the characteristics common to all species. *See In re Curtis*, 354 F.3d 1347, 1355 (Fed. Cir. 2004). A disclosure of a single species may not be sufficient

under the written description requirement when the evidence indicates that a person skilled in the art could not predict the operability of any species other than the one disclosed. *See id.* at 1358. The description relied upon in *In re Curtis*, however, is distinguishable from the present application, in that the description in the Curtis application recited only the common functional properties of the claimed genus and did not provide *any* structural description of the genus. *See id.* at 1355. By direct contrast, as discussed above and herein, Applicants have provided much more, describing structural characteristics that correlate with described functional characteristics.

The Examiner's basis for rejecting the claims for lack of written description appears to rely, in great part, on the possibility that a single amino acid substitution in the BASB082 polypeptide *might* abrogate binding of a specific antibody to that polypeptide. The Examiner asserts that because a single amino acid *may* result in loss of function of a given polypeptide, claims that relate to a recombinant polypeptide comprising an immunogenic polypeptide of 15 or more contiguous amino acids of SEQ ID NO:2 fail to meet the written description requirement. Applicants note that the claim language very clearly and concisely sets forth that the claimed recombinant polypeptide comprises an immunogenic fragment of 15 or 20 or more contiguous amino acids of SEQ ID NO:2; therefore, the immunogenic fragment is an *unsubstituted* fragment of the amino acid sequence set forth in SEQ ID NO:2. Documents that discuss loss of function of different polypeptides when a single amino acid is altered are therefore irrelevant. Moreover, to satisfy the written description requirement, Applicants are not required to describe which, if any, polypeptides are not encompassed by the claims (*i.e.,* a polypeptide that does not exhibit the recited functional characteristic).

If the Examiner is asserting that to meet the written description requirement, Applicants must identify an amino acid that, if altered in SEQ ID NO:2, would significantly reduce the immunogenicity of the polypeptide imposes an unreasonable standard for disclosure of a polypeptide and fragments thereof. Identifying a single amino acid that when substituted abrogates a functional characteristic of a polypeptide, if such an amino acid exists, is far less predictable than identifying polypeptides that retain the associated function. (See *Rochester* at 1360, quoting *In re Storrs*, 245 F.2d 474,478 (1957) ("…while it is necessary that an applicant for a patent give to the public a complete and adequate disclosure in return for the patent grant, the certainty required of the disclosure is not greater than that which is reasonable, having due

regard to the subject matter involved"). Guidance regarding what is reasonable has been provided by the Supreme Court: "The other object of the specification is, to put the public in possession of what the party claims as his own invention, so as to ascertain if he claim anything that is in common use, or is already known, and to guard against prejudice or injury from the use of an invention which the party may otherwise innocently suppose not to be patented" (*Evans v. Eaton*, 20 U.S. (7 Wheat.) 356, 433-34 (1822), quoted by the court in *Rochester*, discussing that "the language of the present statute is not very different in its articulation of the written description requirement" (*see Rochester* at 924-925).

The specification describes the claimed isolated recombinant polypeptides and related fusion proteins and compositions comprising these polypeptides with sufficient, relevant, identifying characteristics to convey to a person skilled in the art that Applicants possessed the claimed embodiments at the time the application was filed. Applicants therefore submit that the claimed subject matter complies with the written description requirement under 35 U.S.C. § 112, first paragraph, and respectfully request that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

The Examiner rejected claims 29, 31, 50, 51, 57, 59, 62, 63, 65, 66, and 68-72 under 35 U.S.C. § 112, first paragraph, asserting that the claimed subject matter is not enabled by the specification. The Examiner states that the rejection is maintained for the reasons asserted in the previous Office Action.

Applicants respectfully traverse this rejection and submit that, contrary to the Examiner's assertions, in view of the abundant guidance and direction provided in the specification, the advanced state of the art, and the high level of skill of a person practicing the art, the specification enables a person skilled in the art to make and use the claimed recombinant polypeptide comprising an immunogenic fragment, as recited, readily and without undue experimentation. (*See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). As noted above in the discussion regarding written description, the pending claims are directed in pertinent part, to an isolated recombinant polypeptide comprising an immunogenic fragment of 15 or more or 20 or more contiguous amino acids of SEQ ID NO:2, wherein the polypeptide is capable of inducing

an antibody that specifically binds to the fragment within SEQ ID NO:2; to related fusion proteins; and to immunogenic compositions comprising the recombinant polypeptides.

Consistent with the purpose of the enablement requirement, the present specification teaches a person skilled in the art how to *make* and *use* the claimed recombinant polypeptide comprising immunogenic fragments, as recited. For example and as previously made of record, the specification teaches an exemplary, detailed polynucleotide sequence and the deduced amino acid sequence of the BASB082 polypeptide (*see, e.g.,* SEQ ID NO:1 and SEQ ID NO:2, respectively). The specification provides detailed guidance for cloning and expressing the claimed recombinant polypeptides (*see, e.g.,* pages 13-16; page 44, last paragraph through page 45; page 47 through page 49, first full paragraph). Furthermore, a person skilled in the art can, routinely and without undue experimentation, determine whether a BASB082 polypeptide immunogenic fragment of 15 or 20 or more contiguous amino acids of SEQ ID NO:2 exhibits the capability to induce production of antibodies that bind specifically to the BASB polypeptide by using any one or more immunoassays, screening methods, and animal models routinely practiced in the art. *See In re Wands,* 858 F.2d 731 (Fed. Cir. 1988) ("Enablement is not precluded by the necessity of some experimentation such as routine screening.") Thus, by using the guidance provided in the specification, a person skilled in the art may routinely, and without undue experimentation, make and use the claimed recombinant polypeptide comprising an immunogenic fragment.

BASB082 is predicted to be an outer membrane protein that may be involved in iron uptake. The BASB082 polypeptide has a predicted leader signal peptide sequence, which would be cleaved after amino acid residue 24 of the sequence set forth in SEQ ID NO:2 (see page 83, Example 1). As is well understood in the art, polypeptides that are membrane bound proteins are translocated through or to the membrane, respectively, by a translocation apparatus that interacts with a signal peptide at the amino terminal end of a nascent polypeptide. A signal peptide sequence is typically cleaved from a nascently translated polypeptide in vivo by a bacterial protease to form the mature polypeptide. Because most (if not all) immunogenic regions that induce production of specific antibodies are located within surface exposed regions of a protein (*see, e.g.,* Roitt et al., *Immunology*, 1998, 4th Edition, Mosby, London, page 7.7 (enclosed herewith for the Examiner's convenience)), a person skilled in the art, using the

exemplary amino acid sequence, SEQ ID NO:2, could use software tools such as PSORT (released in 1991) and Spscan (Wisconsin Sequence Analysis Package, Genetics Computer Group) to predict transmembrane segments and membrane topology of this bacterial outer membrane polypeptide. In addition, based on the understanding that most immunogenic sites are located within surface-exposed regions of a polypeptide, the primary amino acid sequence of a given polypeptide may be used to generate accurate surface contour profiles and predict immunogenic sites (*see, e.g.*, Jameson and Wolf, *Comput. Appl. Biosci.* 4:181-86 (1988), enclosed herewith for the Examiner's convenience).

Additional examples in the art of computational methods that may be used to identify regions of a polypeptide that comprise antigenic determinants include the Hopp and Woods method, which has been in use since 1981 and "has been used widely and has played a vital role in many antigenic structure studies" since then (*see* Hopp, *Peptide Res.*, 6: 183-190, abstract (1993) (enclosed herewith for the Examiner's convenience)). Also routinely practiced at the time the application was filed were computer programs such as a BASIC program called EPIPLOT, which predicts B-cell antigenic sites in proteins from their primary structures by calculating and plotting flexibility, hydrophilicity, and antigenicity profiles using thirteen different scales (see, for example, Menendez et al., *Comput. Appl. Biosci.* 6:101-105 (1990), (enclosed herewith for the Examiner's convenience)). Other exemplary methods include identification of "continuous" antigenic determinants in the protruding regions of proteins (*see, e.g.,* Thornton et al., *EMBO J.* 5:409-413 (1986) (enclosed herewith for the Examiner's convenience)), as well as the prediction of antigenic determinants on protein antigens based on a single parameter, which allowed identification of such determinants with a 75% accuracy rate (*see, e.g.,* Kolaskar et al., *FEBS Lett.* 276:172-74 (1990) (enclosed herewith for the Examiner's convenience)).

Applicants also respectfully disagree with the Examiner's assertions in the previous Office Action (dated October 27, 2008) that the specification must provide predictive criteria for determining "which amino acids or polypeptide fragments are critical to the production of antibodies that recognize said fragment full length [*sic*] SEQ ID NO:2" (*see* page 7). Such a requirement is essentially requiring *a priori* predictability of the outcome, which is not an enablement requirement. The courts have rejected a "reasonable certainty" standard for

enablement disclosure, which is an even lower standard (*see, e.g., In re Angstadt,* 537 F.2d 498, 503 (CCPA 1976) (opining that if *Rainer*, as improperly relied on by the dissent, "stands for the proposition that the disclosure must provide guidance which will enable one skilled in the art to determine, w*ith reasonable certainty before performing the reaction*, whether the claimed product will be obtained…then *all* 'experimentation' is 'undue,' since the term 'experimentation' implies that the success of the particular activity is *uncertain*").

The majority in *Angstadt* also states that a "reasonable certainty" standard goes against the basic policy of the Patent Act, which is to encourage disclosure (*see In re Angstadt* at 503). The court in *In re Angstadt* states that "depriving inventors of claims which adequately protect them and limiting them to claims which *practically invite appropriation of the invention* while avoiding infringement inevitably has the effect of suppressing disclosure." *Id.* at 504 (emphasis added). In a more recent application of these still sound principles, Applicants further note that the test for enablement is not merely quantitative, and that a considerable amount of experimentation is permissible, particularly when great expenditures of time and effort are ordinary in a given field (*See Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006) (quoting the Board of Patent Appeals and Interferences, "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be 'undue' in this [vaccine] art.")).

Applicants strongly disagree with the Examiner's assertion that the claims are not enabled because "[it] is well known in the art that *N. meningitidis* infections are strain and serotype specific and therefore, using claimed polypeptide fragments for all *N. meningitidis* infections is not routine" (*see* Action (dated April 10, 2009) at page 3, last sentence). Determining whether a polypeptide, or fragment thereof, induces an immune response that comprises antibodies that specifically recognize multiple, different strains and serotypes of *N. meningitidis* can be accomplished by any one of several immunochemistry methods and techniques, as well as in vitro and in vivo functional assays (including animal models) that are well known and routinely practiced by a person skilled in the art.

Moreover, the Examiner's assertion pertains more to the ultimate fate of the claimed recombinant polypeptide in clinical development, which is irrelevant to whether the present claims meet the enablement requirement. The Court of Appeals for the Federal Circuit

noted in *In re Brana* (51 F.3d 1560 (Fed. Cir. 1995) that usefulness in the context of pharmaceutical inventions includes the expectation of further research and development, and that efficacy in humans is not necessary for finding a compound useful and enabled under 35 U.S.C. § 112, first paragraph. The court stated, "[t]he stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." The court noted that this principle applies "even though it may eventually appear that the compound is without value in the treatment of humans." *Id.* at 1568, citing *In re Krimmel* (130 U.S.P.Q. 205 (C.C.P.A. 1961)).

In view of the guidance provided in the specification, the scope of the claims, the high level of skill in the art of, and the state of the art, the present application enables a person skilled in the art to make and use, routinely and without undue experimentation, the claimed recombinant polypeptides comprising an immunogenic fragment. Applicants submit that the scope of the claims is commensurate with the disclosure in the specification, satisfying the enablement requirement under 35 U.S.C. § 112, first paragraph, and respectfully request that this rejection be withdrawn.

Applicants submit that all claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If the Examiner believes that a teleconference will facilitate prosecution of the present application, the Examiner is invited to contact the undersigned representative at the phone number provided below.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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